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EXAMINER	
MOSHER, MARY	

ART UNIT	PAPER NUMBER
1648	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,579	ROMMELAERE ET AL.	
	Examiner	Art Unit	
	Mary E. Mosher, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-11,14,15 and 17-20* is/are rejected.

7)☐ Claim(s) *12,13 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). *11*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence printouts.*

Claim construction

Claim 1 has been amended to require that the parvovirus DNA has a left terminus comprising CTWWTCA, the parvovirus DNA is in a vector, and the parvovirus DNA can be excised from the vector in a parvovirus-permissive cell. Reading the specification, it is very difficult to understand what applicant means by "a left terminus". However, an applicant is permitted to omit what is well known in the art at the time of the invention, and the examiner makes reference to a review by Berns to indicate what was well known in the parvovirus art. The specification, on page 3, contains this definition:

> The expression "left terminus" refers to the 3' end of a parvovirus DNA available as a double strand.

This is confusing on its face, because parvoviruses are only available "as a double strand" during replication, when the genome is circular and has no 3' end and no terminus (see Fig. 4 in Berns). However, Fig. 1 in Berns shows 3' terminal nucleotide sequences of the virion strand of parvovirus DNA; the sequence includes a hairpin where the DNA forms a double-stranded region. Therefore, the examiner deduces that "the 3' end of a parvovirus DNA available as a double strand" means the same thing as the 3' terminus of the virion strand of DNA, since the 3' terminal sequence forms a double-stranded hairpin. If this is correct, then the claim requires the parvovirus DNA in the vector to comprise a CTWWTCA sequence in the region that becomes the 3' terminus of the virion strand.

Since the virion strand is the antimessenger strand, a CTWWTCA sequence near the 3' end would become a TGAWWAG sequence near the 5' end in the messenger strand. Therefore, claim 1 is understood to mean that the vector comprises a CTWWTCA sequence near the 3' end of the antimessenger (virion) strand of the parvovirus DNA, which is equivalent to a TGAWWAG sequence near the 5' end of the messenger strand of the parvovirus DNA.

Referring to published parvovirus sequences, it is apparent that the rodent parvoviruses

MVM, H-1, and LUIII all comprise a TGAWWAG sequence near the 5' end of the messenger strand, see the bolded section of the attached sequences. Therefore, any vector comprising the native termini of parvoviruses MVM, H-1, or LUIII (in a form which can excise from the vector in a permissive cell), will meet the claim limitations. This is consistent with applicant's statement on page 6 of the most recent response, that manipulation of a terminal sequence is optional.

Claim Rejections - 35 USC § 112

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. As discussed previously, it is not clear from reading the specification what is meant by "internal replication sequences." Applicant responds that the term is defined by reference to the publication by Tam and Astell. However, an understanding of this phrase is essential to defining the subject matter of this claim. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). Applicant is not required to include in the specification material that is well known in the art; however, the review by Berns does not use this phrase, so it does not appear to be something where the meaning is well known in the art.

Claims 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 requires the vector to have parvovirus DNA originating from H-1 and the left terminus comprises a minimal parvovirus origin of replication of MVM. Amended claim 1

defines a minimal origin of replication as CTWWTCA. Both H-1 and MVM have identical CTWWTCA sequences; both have TGATAAG sequences in the 5' terminus of the messenger strand (equivalent to CTTATCA in the 3' termini of the virion strand). Therefore the "minimal parvovirus origin of replication of MVM" required in claim 8 is found in the native H1 sequence. But parent claim 7 requires the parvovirus DNA to be a combination of sequences of various parvoviruses. Therefore, it is no longer clear what is required in claim 8 (and in parent claim 7), since "various parvoviruses" can have the identical sequence for the minimal origin of replication (as defined by amended claim 1).

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record. Applicant argues that a person skilled in the art would have taken the same steps in connection with different vectors suitable for gene therapy to practice the claimed invention. However, many persons skilled in the art have attempted to "take the same steps in connection with different vectors" and failed (as indicated by the statements regarding the retrovirus vectors as "the first clear success in gene therapy" in the cited publication). Therefore it is maintained that undue experimentation would be required to practice gene therapy using the parvovirus vectors, as claimed.

Claim Objections

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Since CTWWTCA is the consensus sequence of an MVM NS1 nicking site, claim 3 does not further limit parent claim 1 (which requires the CTWWTCA sequence).

Claim Rejections - 35 USC § 102

Claim Rejections - 35 USC § 103

Claims 1-11, 14, 15, 17, and 18 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Maxwell et al 5, 585,254. In response to a 102 rejection based on this patent, Applicant argues that the patent does not teach or suggest the claimed element CTWWTCA sequence. However, Maxwell provides working examples where a vector comprises the termini of rodent parvovirus LuIII, and the parvovirus DNA is able to excise from the vector in a permissive cell. The attached sequence of LuIII indicates that the 5' terminal region of the messenger strand comprises the sequence TGAWWAG; therefore there is reason to believe that the parvovirus vector of the examples inherently meets the claim requirements. Furthermore, Maxwell teaches (but does not provide working examples) of similar vectors comprising MVM and H-1 termini. The termini of these viruses also include the TGAWWAG sequence in the 5' terminal region of the messenger strand, see the attached sequences. Even though Maxwell does not teach the CTWWTCA sequence, this sequence is an inherent characteristic of the materials that Maxwell teaches and suggests. At the very least, it would have been obvious to use known terminal sequences to carry out the suggestions of Maxwell, and since the known sequences comprise the CTWWTCA sequence (in the antimessenger strand), the invention as claimed is seen as at least prima facie obvious, if not anticipated.

Furthermore, since the natural H-1 sequence comprises the same CTWWTCA sequence as MVM, the H-1 embodiment appears to meet the requirements for claim 8 and parent claim 7, since a combination of H-1 DNA with MVM CTWWTCA is identical to the native H-1 DNA with H-1 CTWWTCA. Still further, Maxwell teaches including coding sequences such as cytokines and toxins, see column 11 lines 17-53 for example. Also, Maxwell teaches use of P38 promoter to control expression of the capsid proteins in a helper construct, see column 23 lines 1-26. For these reasons claims 7, 8, 10, 11, 17 are added to this rejection.

Claims 1-6 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tam et al (Virology 193, 812-824, 1993). As discussed above, the normal termini of MVM meet the claim limitations, since they inherently include the CTWWTCA sequence.

Response to Arguments

In addition to the arguments addressed above, applicant argues that the specification provides unexpected results and advantages, that the vectors according to the invention permit higher levels of amplification of the excised genomes, giving up to 1000 times higher titer than conventional packaging systems. This argument is not convincing, because the invention, *as set forth in the claims*, includes conventional packaging systems, as long as the packaged vector includes packaged termini with an endogenous CTWWTCA sequence (such as the unmodified MVM, LUIII, and H-1 termini).

Kestler et al (Human Gene therapy 10:1619-32, 1999, not available as prior art) is cited as of interest. The later publication is similar to the specification in teaching improved replication of parvoviruses, but it differs from the specification in teaching an NS-1 nick site *introduced at the junction between the left-hand viral terminus and the plasmid DNA*. The

examiner has tried and failed to find this concept communicated in the instant specification, so it is NOT suggested that applicant introduce this information by amendment.

Allowable Subject Matter

Claims 12, 13, and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The following is a statement of reasons for the indication of allowable subject matter: The prior art of record does not provide particular motivation to express a chemotactic polypeptide in a parvovirus vector which comprises CTWWTCA in the left terminus (such as a vector constructed from a rodent parvovirus), or to use an SV40-based vector to express the capsid proteins in the same cell as the parvovirus vector which comprises CTWWTCA in the left terminus.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is 703-308-2926 until approximately 1/8/2004, 571-272-0906 afterwards. The examiner can normally be reached on M-T and alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027 until approximately 1/26/2004, 571-272-0902 thereafter. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

12/1/03

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600